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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/526,185	08/03/2005	Gordon D. Ross	3593.1001-008	6460

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EXAMINER	
RICCI, CRAIG D	

ART UNIT	PAPER NUMBER
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/526,185	ROSS ET AL.	
	Examiner	Art Unit	
	CRAIG RICCI	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 February 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,14 and 16-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,14 and 16-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/12/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 02/12/2009 has been entered.

Response to Arguments

2. Applicants' arguments, filed 02/12/2009, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. **Claims 1-4, 14, 16 and 18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to**

enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

5. While Applicant has enabled a method for the treatment of hepatic cancer, breast cancer, colorectal cancer and Non-Hodgkin lymphoma, the specification does not reasonably provide enablement for the treatment of other tumor types. Accordingly, claims **1-4, 14, 16 and 18** are rejected under 35 U.S.C. 112, first paragraph. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

6. Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered, with the most relevant factors discussed below.

7. **Nature of the invention**: The presently claimed invention is directed to a method of suppressing or eliminating tumor cells by administering a therapeutically effective amount of neutral soluble glucan particles and at least one complement-activating anti-tumor antibody directed to the tumor cells or antigens of said tumor cells. Applicant points out that "[i]t is not a single agent that could treat all tumor types but rather a combination of neutral soluble glucan and a complement-activating anti-tumor antibody directed to the tumor cells or antigens of said tumor cells for suppressing or elminating tumor cells… Although the term 'anti-tumor antibody' reflects a general category of

antibodies, a specific antibody is intended for each type of tumor and that antibody is selective or specific to that tumor. Thus, neutral soluble glucan can be combined with a variety of anti-tumor antibodies that are each directed to or specific for a certain type of tumor" (Applicant Argument, Page 5). As such, the invention is complex in that it encompasses a variety of potential combinations (each of which involve a neutral soluble glucan with an anti-tumor antibody specific for a certain cancer to treat that cancer) which can collectively be used to treat tumor cells without limitation.

8. **Breadth of the claims**: The claims are broad in that they encompass a method for suppressing or eliminating tumor cells by administering a therapeutically effective amount of neutral soluble glucan particles and at least one complement-activating anti-tumor antibody. As such, the claims are broad in that they encompass the suppression or elimination of tumor cells without limitation as to the tumor cell(s) to be suppressed or eliminated. Furthermore, the claims are broad in that they encompass numerous combinations of a neutral soluble glucan and an anti-tumor antibody. Thus, the breadth of the claims is extremely broad, which further exacerbates the complexity of the invention.

9. **Guidance of the specification/The existence of working examples**: The amount of direction provided by the Applicant is considered to be determined by the specification and the working examples. As evidence of the variety of specific antibodies encompassed by instant claim 1, each of which is selective and specific for a single type of tumor, Applicant discloses 6 examples: **HERCEPTIN®** (a.k.a., trastuzumab); **RITUXAN®** (a.k.a., rituximab) (Page 33); **3F8** (Page 52), **14.G2a** (Page

52-53); **11C1** (Page 53); and **BCP8 anti-MUC1** (Page 55) as well as **cetuximab** (Instant claim 2) and which appear to be specific for hepatic, mammory, colorectal, and Non-Hodgkin lymphoma. As to other specific antibodies which are selective and specific for other tumors, Applicant states that "[t]he number of candidate antibodies is described in the Specification (See page 19, line 24 to page 23, line 19) and thus do not include all antibodies but a narrowed class defined by the characteristics described" (Applicant Argument, Page 5). It is noted that the cited pages disclose a process for producing whole glucan particles, and do not disclose any candidate antibodies. Moreover, the only other disclosure of "candidate antibodies" appears to be the description of various protocols that can be employed to identify potential antibodies. Yet, no specific antibodies that are directed to the other tumor or tumor antigens that are able to activate one or more members of the complement cascade are described.

10. **State of the art/Predictability of the art**: The level of predictability in the art is considered to be relatively low. As noted by online at *cancerbackup.org*, "it is very difficult find antigens that are specific only for cancer cells as most of the antigens found on cancers are also found to a lesser extent on normal tissues" and at *breastcancer.org*, "there are two serious obstacles with the use of antibodies to target cancer cells. First, the size of the antibodies is important relative to the size of the cells. Some cancer cells are destroyed only if the antibody molecules can penetrate the cells' outer (and sometimes inner) barriers. If they're too big, the antibodies may not be able to get INTO the cells. The second problem is that with each generation of cancer cells that form, it's

hard to make antibodies that work effectively against all of the different kinds of cells that make up the cancer."

11. **Amount of experimentation necessary**: Given the complex nature of the invention, which is exacerbated by the breadth of the claims, and given the lack of working examples and the high degree of unpredictability in the art, it would require undue experimentation for a person of ordinary skill in the art to make the invention as claimed. Specifically, the invention is drawn to a method of suppressing or eliminating tumor cells (without limitation) by administering a therapeutically effective amount of neutral soluble glucan particles and at least one complement-activating anti-tumor antibody directed to the tumor cells or antigens of said tumor cells. Moreover, the method encompasses numerous combinations comprising distinct complement-activating anti-tumor antibody or antibodies which are selective and specific for a single tumor. Yet, Applicant has not disclosed antibodies which are selective and specific for each of the tumors encompassed by the claims. And, furthermore, it is clear that the art has not progressed to the point where one of ordinary skill would be able to produce a tumor-specific antibody selective and specific for a single tumor and which is able to activate one or more members of the complement cascade in that tumor using the methodology disclosed, absent undue experimentation.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. **Claims 1-4, 14, and 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Vetvicka et al* (J Clin Invest 98:50-61, 1996), *Jamas et al* (US 5,488,040), *Hortobagyi* (Semin Oncol 28:43-47, 2001), *Sliwkowski* (Semin Oncol 26:60-70, 1999 as evidenced by *Gelderman et al* (TRENDS in Immunol 25:158-164, 2004), and *Kolb et al* (US 5,221,616).**

15. Instant claim 1 is drawn to a method of suppressing or eliminating tumor cells, comprising administering to a subject in need of suppressing or eliminating tumor cells a neutral soluble glucan and at least one complement activating anti-tumor antibody directed to the tumor cells or antigens of said tumor cells, wherein the glucan does not induce inflammatory cytokines and the glucan and antibody together suppress or eliminate tumor cells.

16. It is well known in the art, as evidenced by *Vetvicka et al*, that iC3b-coated tumor cells are not targeted for destruction by natural killer cells (Page 50, Column 2).

However, soluble β-glucans cause natural killer (NK) cells "to express potent tumoricidal activity" (Page 50, Column 2) by "priming" the CR3 receptors of NK cells "for cytotoxicity of iC3b-tumor cells that were otherwise resistant to killing" (Page 51, Column 1). Notably, *Vetvicka et al* also disclose that "[e]xperiments have now shown that the density of bound iC3b/C3dg on freshly isolated breast tumors is adequate for *in vitro* recognition and cytotoxicity of SZP-primed CR3. In experiments with mice, SZP therapy caused regression of established mammary tumors" (Page 59, Column 2). Thus, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to administer soluble β-glucans to suppress or eliminate mammary tumor cells to a subject in need thereof in view of *Vetvicka et al*. The skilled artisan would have been motivated to do since *Vetvicka et al* teach that (1) soluble β-glucans prime NK cells for cytotoxicity of iC3b-tumor cells; (2) mammary carcinoma cells contain sufficient iC3b for recognition by CR3-primed NK cells; and (3) STZ (which similarly primes CR3 of NK cells (Page 59, Column 2)) can treat mammary tumors. Accordingly, the skilled artisan would have reasonably predicted that administration of soluble β-glucans would prime CR3 of NK cells for cytotoxicity of iC3b-tumor cells and specifically mammary carcinoma cells, thus treating mammary tumors.

17. However, *Vetvicka et al* do not explicitly teach the administration of **neutral** soluble glucans as recited by instant claim 1. Nor do *Vetvicka et al* teach the administration of at least one complement activating anti-tumor antibody as recited by instant claim 1.

18. **FIRST**, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to administer neutral soluble glucans, specifically, as opposed to soluble glucans (as taught by *Vetvicka et al*) in view of *Jamas et al*. *Jamas et al* disclose that the administration of soluble β-glucans (but not neutral soluble glucans) stimulate cytokines such as tumor necrosis factor (Column 2, Lines 39-55) which is "involved in infection, inflammation and **cancer**" (Column 3, Lines 14-15, emphasis added). As such, it would have been *prima facie* obvious to administer **neutral** soluble glucans (as taught by *Jamas et al*) instead of soluble glucans to suppress or eliminate mammary tumor cells (as taught by *Vetvicka et al*). The skilled artisan would have been motivated to do so in order to prime NK cells for cytotoxicity of iC3b-tumor cells (e.g., mammary tumor cells) while avoiding the adverse side affects caused by the stimulation of tumor necrosis factor (i.e., cancer) with a reasonable expectation of success considering that *Jamas et al* specifically teach that neutral soluble glucans retain "a specific subset of immunological properties common to β-glucans but uniquely do not induce production of IL-1 and TNF *in vitro* or *in vivo*" (Column 3, Lines 45-48).

19. **SECOND**, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to also administer at least one complement activating anti-tumor antibody as recited by claim 1 for each of the following reasons: **(1)** complement activating anti-tumor antibodies, such as trastuzumab (a monoclonal antibody), are well known in the art for the treatment of cancer, including mammary carcinoma, as evidenced by *Hortobagyi* (Abstract). As stated in MPEP 2144.06, "It is

prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626, F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). Accordingly, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to also administer at least one complement activating anti-tumor antibody, specifically trastuzumab, in view of *In re Kerkhoven*, with a reasonable expectation of success. And **(2)**, *Sliwkowski* et al teach that trastuzumab activates complement, as evidenced by *Gelderman et al* (Page 160, Column 1, Reference 15). Since iC3b is generated during activation of the complement system (as evidenced by *Kolb et al* (Column 3, Lines 3-8)), the skilled artisan would have reasonably predicted that the co-administration of trastuzumab would promote iC3b coating of tumor cells, thus enhancing the targeting of neutral soluble glucan CR3-primed NK cells for cytotoxicity of the iC3b-coated tumor cells. Accordingly, it would have been *prima facie* obvious to a person of ordinary skill in the art to administer a neutral soluble glucan and at least one complement activating anti-tumor antibody (trastuzumab) to a subject in need thereof.

20. Thus, for all of the foregoing reasons, instant claims 1-3 and 16-18 are rejected.

21. Instant claim 4 is drawn to the method of claim 1 wherein the soluble beta glucan is administered parenterally. As disclosed by *Jamas et al*, "[t]he neutral soluble glucan preparation is appropriate for parenteral... administration" (Column 4, Lines 1-3).

Accordingly, it would have been *prima facie* obvious to a person of ordinary skill in the art to administer the soluble beta glucan is parenterally

22. Instant claim 14 is drawn to the method of claim 1 wherein the neutral soluble glucan is in a single and/or triple helix conformation. Significantly, the neutral soluble glucans taught by *Jamas et al* are in the triple helix conformation (Column 3, Lines 54-55).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CRAIG RICCI whose telephone number is (571) 270-5864. The examiner can normally be reached on Monday through Thursday, and every other Friday, 7:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/CRAIG RICCI/
Examiner, Art Unit 1614

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